REMARKS

Status of Claims

Claims 1-9 and 12-95 are pending in the application. Claims 21-23, 32-34, 38-51, 65-67, 76-78 and 82-95 have been withdrawn from consideration. Claims 24, 35, 68 and 79 have been cancelled. Claims 1-9, 12-20, 24-31, 35-37, 52-64, 68-75 and 79-81 have been rejected.

CLAIM REJECTIONS

35 U.S.C. § 103 Rejections

In the Office Action, the Examiner rejected claims 1-9, 12-20, 24-31, 35-37, 52-64, 68-75 and 79-81 under 35 U.S.C. § 103(a), as allegedly being rendered obvious in view of the combined teaching of Tucker (US 4,636,505) and Miller et al (WO 98/55153). Applicants disagree.

In the response filed January 2, 2008, Applicants stated that the metabolism of O-bridged SARMs and S-bridged SARMs compounds differs substantially, and that O-bridged and S-bridged compounds are not equivalent. The Examiner has not responded to Applicants' comments and Applicants' respectfully request that the Examiner consider the arguments and address them with specificity.

In particular, in response to the rejection, the Examiner has no basis for his contention of the interchangeability of S-bridged and O-bridged metabolites.

> "To establish a *prima facie* case of obviousness, ... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (To establish a *prima facie* case of obviousness, the Examiner must "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious") (*quoting In re Rouffet*, 149 F.3d 1350, 1357-59 (Fed. Cir. 1998)), *reh'g en banc denied*; *Teleflex, Inc. v. KSR Int'l Co.*, 119 Fed. Appx. 282, 285; 2005 U.S. App. LEXIS 176, *7 (*unpub'*) (Fed. Cir. 2005), *cert. granted*.

The Examiner alleged that Tucker, in column 9, teaches that O-bridged and S-bridged acylanilides are equivalent. Applicants disagree. Column 9 is merely a listing of compounds

presented in the application; no data is presented which specifically demonstrates their equivalence. In our previous two responses, however, Applicants described a concrete example (Example 5) in the subject Application, **demonstrating that the metabolism of O-bridged SARM compounds differs substantially from that of S-bridged compounds** presented in Tucker. Moreover, the Applicants' have provided evidence showing concrete differences in the metabolism of O-bridged versus S-bridged SARMs compounds. The Examiner has not provided any basis for his contentions of obviousness and thus has not established a prima facie case.

Example 5 demonstrates that Bicalutamide is metabolically different from the claimed structures and is converted from exhibiting agonist to antagonist activity as a function of metabolizing the compound, resulting in the oxidation of the thioether linkage to a sulfonyl linkage (see Perera et. al, *Drug metabolism and Disposition*, vol. 34(10), 1713-1721, 2006, previously attached as Appendix 1). Furthermore, Applicants noted to the Examiner that the lack of a substituted phenyl ring in Tucker's O-bridged compounds would likewise result in different metabolites (see for example, C.E. Bohl et. al. in *J. Biol. Chem.* vol. 280, No. 45, p. 37747, 2005, attached previously as Appendix 2). The Examiner has not provided any evidence to rebut the Applicants' evidence, and thus has not established a prima facie case.

Furthermore, it would not have been obvious to one of ordinary skill in the art, based on Tucker, to obtain the claimed metabolites of the substituted O-bridged compounds since Tucker does not disclose nor provide any basis for the role of the O-bridge moiety, which impart the characteristics to the claimed compounds of Applicants' invention. Certainly Tucker provides neither a description nor a foundation for metabolites of such compounds. Moreover, Applicants have specifically demonstrated in the subject Application that O-bridged and S-bridged substituted acylanilides yield different metabolites, and that such metabolites differ structurally and functionally, thus Tucker cannot render obvious the claimed O-bridged metabolite compounds.

For instance, Tucker does not indicate that the major metabolite of O-bridged SARM compounds are the hydroxylated metabolite (oxidation), the hydrolyzed metabolite, the

deacetylated metabolite (for compound IV) or the aminated metabolite. Thus, the metabolites of Compounds I, II, III, IV, VII, VIII, IX, X are not obvious.

Likewise, Tucker does not demonstrate that it yields the compounds of the instant invention. Applicants have shown that the S-bridged compounds of Tucker could not yield the same metabolites as the O-bridged compounds of the instant invention, Certainly, Tucker does not lead the one of ordinary skill in the art to the hydroxylated, deacetylated, or aminated derivatives of the compounds of formulas I, II, III, IV, VII, VIII, IX, X, as claimed in the present invention. Accordingly, the metabolites cannot be rendered obvious in view of Tucker.

Moreover, the literature supports that the substitution of the phenyl ring affects the pharmacologic activity of the O-linked compounds, as presented in Kim J., *et al. J. Pharm. and Exper. Therapeutics*, 2003, vol 315(1): 230-239. (*See* Table 4 of the Kim reference).

In addition, S-bridged compounds are metabolically converted to sulfide linked derivatives that are pure antagonists, which limits the *in vivo* activity of the S-linked compounds and diminishes prostate, seminal vesicle and *levator ani* weights (*see* Yin., *et al. J. Pharm. and Exper. Therapeutics*, 2003, vol 304, 1323-1333, illustrating the manner in which S-linked compounds are metabolized to inactive or antiandrogenic metabolites) The O-bridged compounds of the instant invention, however, are selectively anabolic which is unexpected in view of the S-bridged compounds activity. Such a finding is unexpected. The ability of O-bridged SARMs to both inhibit the prostate and concurrently promote muscle weight gain provides an unexpected advantage, and is unprecedented in Tucker.

Tucker discloses only the use of acylanilides as antiandrogenic agents, and does not disclosed ore render obvious that the compounds may have androgenic or anabolic activity, much less tissue-selective anabolic and androgenic activity.

Accordingly Tucker cannot render obvious the metabolites of formulas I, II, III, IV, VII, VIII, IX, X, as claimed in the present invention, and applicants request withdrawal of the rejection.

The Examiner alleged that Miller renders the claimed invention obvious, when viewed in combination with Tucker. Applicants disagree and assert that the cited reference (Miller) is disqualified as prior art under 35 U.S.C. 103(c), since the subject matter which was cited as prior art to the claimed invention were commonly owned at the time the claimed invention was made.

Applicants submit a statement issued by the attorney of record indicating the common ownership of WO 98/55153 and the subject Application, at the time the instant invention was made. The Statement reflects the common ownership of WO 98/55153, which lists the University of Tennessee Research Foundation (UTRF) as the Applicant, and the subject Application, listing UTRF as the Assignee of Record.

Accordingly, claims 1-9, 12-20, 24-31, 35-37, 52-64, 68-75 and 79-are not obvious in view of the combined teaching of Tucker (US 4,636,505) and Miller et al (WO 98/55153), and Applicants request withdrawal of the rejection.

Double Patenting Rejections

In the Office Action, the Examiner rejected claims 1-9, 12-20, 24-31, 35-37, 52-64, 68-75 and 79-81 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-85 of US 6,838,484 or over claims 1-10 of US 6,569,896 or over claims 1-5 of US 6,492,554. Applicants submit that the cited references are directed to O-bridged acyl-anilides which are not essentially identical in scope with the specifically claimed metabolites, and do not comprise overlapping claim scope. For example, none of the cited references specifically claim a compound of the formula IX wherein $N(R)_2$ is NHOH, NO, $NHOSO_3$ or NHO-glucuronide. None of the patents specifically disclose compounds

which are hydroxylated, glucuronidated, or sulfonated. Applicants respectfully disagree with the rejections.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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STATEMENT OF COMMON OWNERSHIP FOR WORLD INTELLECTUAL PROPERTY ORGANIZATION PUBLICATION NUMBER WO 98/55153 AND UNITED STATES PATENT APPLICATION SERIAL NUMBER 10/849,039, UNDER MPEP 706.02(l)(2)

I, Mark Cohen, the attorney of record for the subject Application, hereby attest to the fact that World Intellectual Property Organization Publication Number WO 98/55153 is commonly owned by the University of Tennessee Research Foundation with United States Patent Application Serial Number 10/849,039 assigned to the University of Tennessee Research Foundation, and that both WO 98/55153 and United States Patent Application Serial Number 10/849,039 were thus all commonly owned at the time the invention was made.

Mark S. Cohen
September 18, 2008